

Approach to the Patient with Nephrolithiasis; The Stone Quiz

Farahnak Assadi*¹, MD

1. Pediatric Nephrologist, Rush University Medical Center, Chicago, IL, USA

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Abstract

Calcium oxalate stones are the most common type of stones in patients with idiopathic nephrolithiasis. Calcium phosphate stones are more typical of patients with renal tubular acidosis, chronic urinary tract infection and primary hyperparathyroidism.

A non-contrast enhanced helical computed tomography (CT) scan of the abdomen is the diagnostic procedure of choice with superior sensitivity and specificity of almost 100% compared to the KUB and abdominal ultrasound. Patients should be instructed to strain their urine and bring in any stone that passes for analysis. Stone identification enables better planning of subsequent therapy. The likelihood of stone passage is 95% for stones up to 5 mm in size. Stones larger than 5 mm in diameter that do not pass in several days merit referral to a urologist for lithotripsy, or lithotomy. No specific work-up or drug therapy is typically provided for patients who have passed a single stone. Long term management of patients who have passed their first stone includes recommendations to avoid a diet high in salt or animal protein and maintenance of a fluid intake greater than 2 liters per day. A low calcium diet is also an important risk factor for calcium nephrolithiasis. A low dietary calcium intake reduces the concentration of calcium in the intestinal lumen which can lead to increase in gastrointestinal absorption and urinary excretion of oxalate. Patient with recurrent disease should receive a complete evaluation to treat the identified risk factors and prevent stone formation.

Key Words: Nephrolithiasis, Stone, Urine, Hypercalciuria

Introduction

Nephrolithiasis is a common disease with a prevalence of 5 to 10 percent by the age of 60 years. It is higher in men than in women. Most stones, approximately 75-80%, are calcium stones, mostly calcium oxalate and less calcium

phosphate. In patients with a propensity for calcium stone formation, the principal determinant of whether the stone will be calcium oxalate or calcium phosphate is the urine pH. Oxalate stones tend to form in relatively acid urine while phosphate stones form in alkaline urine. For this reason, patients with

* Correspondence author;

Address: Rush University Medical Center, 1725 West Harrison St, 718 Professional Bldg, Chicago, IL, USA

E-mail: fassadi@rush.edu

predominately calcium phosphate stones should be evaluated for conditions associated with alkaline urine such as renal tubular acidosis, urinary tract infection, and hyperparathyroidism. Other stone types include uric acid, struvite (magnesium ammonium phosphate) and cystine. Stone formation appears to be due to super saturation of the urine with normally soluble material such as calcium.

Clinical Presentation

Stones may present as attacks of colic, or present with crystalluria, hematuria, silent obstruction, or as an asymptomatic finding on routine abdominal x-ray.

Stones are painless as long as they are attached to the renal papilla. Once they break loose, stones produce symptoms as they pass from the renal pelvis into the ureter, obstructing the flow of urine and causing an acute attack of pain, called renal colic. The site of obstruction usually determines the location of pain. Upper ureteral obstruction causes flank pain while lower obstruction leads to pain that may radiate to the testicle or labia. Stones entering the bladder may be associated with dysuria and frequency. The pain characteristically is extremely severe.

Physical examination typically reveals flank tenderness and occasionally a palpable, tender kidney. Bowel sounds are usually hypoactive and there may be a mild ileus.

Differential Diagnosis

The combination of complaints of nausea and vomiting, severe abdominal pain, and flank pain that radiates to the groin may suggest any of several disease processes. These signs and symptoms could be explained by kidney-ureteral inflammation or obstruction such as nephrolithiasis or sloughed renal papillary necrosis, other medical conditions such as loin pain-hematuria, diverticulitis, appendicitis, diverticulitis, irritable bowel syndrome, colitis or intestinal obstruction.

Laboratory Testing and Diagnostic Studies

In a patient with flank pain radiating to the testicle or labia and nausea and vomiting, a complete blood count should be obtained to determine infection, inflammation, anemia of chronic disease, and/ or bleeding.

A urinalysis that is positive for leukocytes and bacteria would speak for infection, whereas hematuria may be a sign of stone, infection, tumor, trauma, sloughed papilla, or bleeding. Patients with stone disease are likely to have concentrated urine and may even show crystals in their urinalysis. A vary alkaline urine argues against active uric acid or cystine stone disease. Electrolytes and blood urea nitrogen are needed to assess the metabolic status of a patient with nausea and vomiting and will also be useful in evaluating possible renal disease.

Measurements of serum calcium, phosphate, uric acid, and albumin concentration are indicated when the differential diagnosis includes the possibility of nephrolithiasis. The measurement of albumin is necessary to be able to evaluate the total calcium concentration.

The diagnosis of nephrolithiasis is initially suspected by the clinical presentation and confirmed radiologically. Acute unilateral flank pain without abdominal tenderness, hematuria, and a positive plain film of the abdomen are present in 90 percent of emergency room patients presenting with stone.

A flat plate of the abdomen (KUB) and/or abdominal ultrasound are non-invasive studies that should be done initially. They will allow detection of the majority of renal stones and provide information relative to intestinal pathology. A KUB will miss radiolucent uric acid stones, *may* miss small stones, and will not detect urinary obstruction.

If the KUB is negative, a non-contrast-enhanced helical computed tomography (CT) scan of the abdomen is then performed. The CT scan is the diagnostic procedure of choice, is slightly more expensive than intravenous pyelogram (IVP) but is faster than IVP, with superior sensitivity and specificity of almost 100%.

Initial Management Plan

Most attacks of renal colic can be managed expectantly with pain relief and increased fluid intake. Both parenteral non-steroidal inflammatory drugs and narcotics have been used for pain control. In one study, intravenous katabolic was associated with improved pain relief compared with intravenous meperidine.

Patients should be instructed to strain their urine and bring in any stone that passes for analysis. Stone identification enables better planning of subsequent therapy.

Patients can be managed at home if pain relief is obtained and they tolerate oral intake. Hospitalization is required for those who cannot tolerate oral intake or have severe pain which is difficult to control. Urology consultation is indicated in patients with complete obstruction, acute renal failure, or urosepsis.

The size of stone is an important prognostic factor as follows:

The likelihood of stone passage is 95% for stones up to 5 mm in size; larger stones most often do not. A renal ultrasound should be performed one week after stone passage to ensure that there are no residual stones or fragments.

Stones 4 mm in diameter or smaller can be managed expectantly up to 2 weeks. Stones larger than 5 mm that do not pass in several days merit referral to a urologist. Intervention, most commonly with shock wave lithotripsy, endoscopic lithotripsy, open lithotomy or percutaneous nephrolithotomy is indicated for continued severe pain, bleeding obstruction, or serious infection.

The likelihood of passage of a second stone is less than 50% at 10 years but approaches 75-100% by 15-20 years. For this reason, no specific workup or drug therapy is typically provided for patients who have passed a single stone, unless the initial evaluation suggests an inherited stone disease, renal disease or multiple stones. In addition, it is reasonable to institute therapy in patients at higher risk for recurrence such as patients with a family history of stones and patients with stones composed of cystine, uric acid, calcium phosphate or struvite.

Long-term management of patients who have passed their first stone includes recommendations

to avoid a diet high in salt or animal protein and maintenance of a fluid intake greater than 2 liters/day. Both high sodium intake and high protein intake increase the urinary excretion of calcium and a high protein intake is also associated with urinary acidification and increased uric acid excretion, all of which are risk factors for stone formation. Increasing fluid intake to greater than 2 liters/day can reduce the risk of substantial stone formation by up to 50 percent.

Patients with recurrent disease should receive a complete evaluation and specific therapies designed to treat the identified risk factors and prevent stone formation. The identification of risk factors and the management of patients with recurrent nephrolithiasis depend upon the identity of the stone. Ideally, patients who have passed a stone have retrieved the stone for analysis. In the absence of this analysis, identification is based upon the following:

Cystine Stones

Patients typically have a positive family history and exhibit the presence of cystine crystals upon urinalysis. The diagnosis is made by measurement of urinary cystine excretion.

Uric Acid Stones

These patients characteristically have radiolucent stones and persistently acid urine.

Struvite Stones

These stones only form in patients with a chronic urinary tract infection. The urine is typically alkaline and affected patients often have multiple triple phosphate crystals in the urine. The stones can grow rapidly and may develop into a staghorn or branched calculus.

Calcium Stones

Stones composed purely or predominantly of calcium phosphate are associated with the same risk factors as calcium oxalate stones (other than hyperoxaluria and hyperuricosuria). However, it is important to note that calcium phosphate stones are more typical of patients with an acidification defect. This can occur in complete or incomplete type 1 (distal) renal tubular acidosis in which the urine pH is persistently

above 5.3, even after an acid load, chronic urinary tract infection and primary hyperparathyroidism. For this reason, patients who pass predominantly calcium phosphate stone should undergo evaluation for these conditions.

Several 24 hr urine collections should be obtained to evaluate the presence or absence of treatable metabolic risk factors. In many laboratories, two or three separate collections are required to obtain all of this information: uric acid is measured in a plain or alkaline solution; calcium and oxalate in hydrochloric or nitric acid, and citrate in an acidified solution.

Hypercalciuria: Increased urinary calcium excretion ($> 4 \text{ mg/kg/24 hrs}$) occurs in 50-60% of patients with recurrent calcium stones. Hypercalciuria can occur due to increased filtered load (hypercalcemia) or reduced tubular reabsorption. The latter can be caused by decreased secretion of parathyroid hormone, chronic metabolic acidosis, or phosphate depletion. Known causes typically account for up to 5% of patients with recurrent calcium stones and hypercalciuria. In the remainder 95%, the condition is called idiopathic hypercalciuria.

Treatment of idiopathic hypercalciuria consists of the administration of thiazide diuretics (12.5-25 mg/day) and moderate dietary salt restriction. Thiazide diuretics reduce urinary calcium excretion because of two effects upon tubular transport. Extracellular fluid (ECF) volume contraction secondary to inhibition of sodium reabsorption in the distal convoluted tubule (DCT) leads to stimulation of proximal tubular sodium reabsorption in an attempt to repair the volume contraction. As calcium reabsorption in proximal tubule is linked to sodium reabsorption, there is a parallel enhancement of calcium reabsorption. In addition, thiazide diuretics directly stimulate the reabsorption of calcium in DCT. The net effect is a reduction in urinary calcium excretion of approximately 50%. Excess sodium intake can blunt the effectiveness of this treatment, as a significant portion of the reduced urinary calcium excretion is dependent upon the production of ECF volume contraction. For this reason, moderate dietary sodium restriction should be instituted. Amiloride has similar effects and can be used in addition to thiazide diuretics.

Hyperuricosuria: An increase in urinary uric acid excretion ($>750 \text{ mg/24 hrs}$) can promote calcium stone formation. This may be due to the formation by the uric acid crystals of a nidus for subsequent calcium oxalate or calcium phosphate precipitation.

Hyperuricosuria is seen in up to 20-25% of patients with recurrent calcium nephrolithiasis. In most of these patients, a high purine diet rather than a defect in uric acid metabolism is responsible for the enhanced uric acid formation and excretion. If dietary modification is ineffective, patients with hyperuricosuria can be effectively treated with allopurinol (50 to 300 mg/day).

Hypocitraturia: Urinary citrate acts in the tubular lumen by combining with calcium to form a non-dissociable but soluble complex. As a result, there is less free calcium available to combine with oxalate and crystal formation is inhibited.

The principal determinant of urinary citrate excretion is acid-base balance. Chronic acidosis enhances the proximal tubular reabsorption of citrate and reduces urinary citrate excretion. There are several potential conditions associated with hypocitraturia ($<320 \text{ mg/24 hrs}$):

- Renal tubular acidosis
- Diarrhea with chronic metabolic acidosis
- Carbonic anhydrase inhibitors

Hypocitraturia occurs in approximately 20-25% of patients with recurrent calcium nephrolithiasis; it typically occurs in these patients in the absence of changes in acid-base balance, so called "idiopathic" hypocitraturia. Incomplete type 1 (distal) renal tubular acidosis may account for at least part of the pool of these patients.

Citrate excretion can be enhanced by alkalinizing the plasma by the daily administration of 30 to 80 mEq of potassium citrate or potassium bicarbonate.

Hyperoxaluria: An increase in urinary oxalate excretion ($>45 \text{ mg/day}$) occurs in 10-20% of calcium stone formers. Normally, dietary oxalate only accounts for 10% of urinary oxalate excretion: Urinary oxalate is principally derived from metabolism of glycine and ascorbic acid. This is because dietary oxalate is bound by calcium to form insoluble calcium oxalate within

the intestinal lumen. Intestinal oxalate absorption and urinary oxalate excretion are increased in those conditions in which intestinal calcium concentration is reduced which include:

Low calcium diet

Absorptive hypercalciuria: Malabsorption of fatty acids and bile salts (enteric hyperoxaluria). This condition associated with small bowel disease or surgical resection leads to binding of calcium to bile salts and reduced availability for binding oxalate. The unbound oxalate is then absorbed in the colon.

High dietary vitamin C intake - Increased urinary oxalate excretion has been associated with megadose vitamin C therapy but it is not clear if vitamin C ingestion is a risk factor for calcium stones. Some investigators recommend limiting vitamin C to less than 2 g/day in patients with recurrent calcium oxalate stones.

Risk Factors for Calcium Stone Formation

High dietary protein intake: The metabolism of sulfur-containing amino acids increases the daily acid load by generating sulfuric acid. Animal protein is much more likely to induce this effect than vegetable protein, since it has a higher sulfur content and therefore generates more acid. The production of acid and uric acid from protein metabolism has deleterious effects upon urinary excretion of calcium, citrate, and uric acid. In one study in normal individuals for example, a low carbohydrate, high protein diet resulted in the following changes in urinary excretion:

- Urine pH decreased from 6.09 to 5.56 and net acid excretion increased by 56 mEq/day
- Urinary citrate levels decreased from 763 mg/day to 449 mg/day
- Urinary saturation of un-dissociated uric acid increased more than twofold
- Urinary calcium levels increased from 160 mg/day to 258 mg/day

Lowering protein intake in patients with recurrent calcium nephrolithiasis to about 1 g/kg/day will produce favorable changes in the urine and is an important aspect of the therapeutic regimen.

High dietary sodium intake: A high sodium intake will increase the urinary excretion of

calcium. This is because the reabsorption of calcium passively follows that of sodium and water in the proximal tubule. An increased dietary sodium intake leads to ECF expansion and compensatory decreases in proximal sodium reabsorption, a parallel reduction in calcium transport and increased calcium excretion. An increase in dietary sodium intake of 100 mEq/day can lead to an increase in urinary calcium excretion of 100 mg/day.

Low fluid intake: A low fluid intake is an important risk factor by increasing the urinary concentration of calcium and oxalate as well as slowing the urine flow rate. Patients with stone disease should be encouraged to drink more than 2 liters per day water. Soft drinks acidified with phosphoric acid may increase the risk of stone disease and should be avoided.

Low dietary calcium intake: A low calcium intake reduces the concentration of calcium in the intestinal lumen. This reduction in calcium concentration leads to increase in gastrointestinal absorption and urinary excretion of oxalate. For this reason, several studies have shown that a low calcium diet is an important risk factor for calcium nephrolithiasis and is contraindicated in the management of these patients.

Uric acid stone

The vast majority of patients with recurrent uric acid stones do not have an identifiable abnormality in uric acid metabolism; plasma and urinary uric acid excretion are normal in over 80%. Rather, uric acid stones form in these patients due to a defect in production of ammonia such that the urine pH is persistently acid with resultant uric acid precipitation. Other risk factors are a hot climate with reduced fluid intake and dehydration associated with metabolic acidosis as in chronic diarrhea states. In another 10-20%, typically patients with gout, there is overproduction of uric acid and increased uric acid excretion.

Uric acid nephrolithiasis is treated principally with increased fluid intake (>2.5 liters/day) and alkalization of the urine. Alkalinization of the urine to a pH of 6.75 (1 pH unit above the pKa for uric acid) will lead to 90% of the total urinary uric acid being in the form of the more soluble urate salt. Treatment with either potassium

bicarbonate or potassium citrate (1-2 mEq/kg/day) will often lead to dissolution of preexisting stones and will also prevent the formation of new stones. Acetazolamide can be used to alkaline urine pH in patients with hyperuricosuria who do not response to oral alkali therapy or those with metabolic alkalosis in whom oral alkali therapy is contraindicated. Allopurinol can be used to lower uric acid production and subsequent excretion in patients with hyperuricosuria who do not respond to hydration and alkali therapy.

Struvite Stones

Struvite stones are composed of a combination of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite. Struvite stone formation occurs only when ammonia production is increased and the urine pH is elevated which decreases the solubility of phosphate. Infection with a urease producing organism (*Proteus*, *Klebsiella*) leads to breakdown of urinary urea to ammonia and CO₂. Ammonia alkalinizes the urine and there is precipitation of ammonium phosphate with calcium and magnesium.

Struvite stones may grow rapidly and can develop into a staghorn or branched calculus involving the entire renal pelvis and calyces. Medical treatment alone is typically unsuccessful and most patients require definitive surgical treatment for stone removal. Percutaneous nephrolithotomy alone or in combination with shock wave lithotripsy is the treatment of choice.

Cystine Stone

Cystinuria is an autosomal recessive disorder of renal tubular amino acid transport. There is an impaired transport of four dibasic amino acids (cystine, ornithin, argentine, and lysine [COLA]). The clinical manifestations of the disorder are due to the relative insolubility of cystine and subsequent stone formation.

The normal cystine excretion is 30 mg/day; the solubility of cystine is approximately 300 mg/liter. Treatment is aimed at reducing the level of cystine concentration to less than 300 mg/liter with high fluid intake and increasing the solubility of cystine with urine alkalization. A significant increase in solubility requires the achievement of urine pH greater than 7.0. This

requires 3-4 mEq/kg/day of potassium citrate or potassium bicarbonate with or without acetazolamide.

Several drugs act by forming a soluble disulfide with cystine decreasing the availability of free cystine to form cystine. These include penicillamine (1-2 g/day), tiopronin, and captopril. Penicillamine is the most efficacious and is the drug with the most clinical experience in this condition but its use is often limited by side effects.

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Nephrolithiasis

CLINICAL QUIZ

CASE 1: A 17-year old boy present to the emergency room with pain radiating to the right testicle. The pain began as a dull ache in the right flank approximately 6 hours ago while he was sitting at his desk at school. The pain rapidly progressed increasing in intensity steadily over a period of 1 hr. It was subsequently associated with radiation along the inguinal canal into the groin and the right testicle. This is the first time the patient was experiencing these symptoms. He does admit some nausea and vomiting in the last several hours but he denies chills, fever, dysuria or urgency. Current medication includes atenolol 25 mg once daily for mild hypertension. On examination the vital signs are normal. He weighs 70 kg. Examination of HEENT is normal. The chest is clear to auscultation and percussion. The heart size is normal and there are no murmurs. The abdomen is soft, non-tender, and slightly distended with hypoactive bowel sounds. There is no organomegaly, no masses, rebound or guarding. No bruits are heard and there are no hernias. There is moderate cost vertebral angle tenderness to palpation on the right side. There is no edema. Laboratory studies show Hb 14 g/dl; Hc 44%; WBC 5600 cells/μl; sodium 140 mEq/l; potassium 4 mEq/l; chloride 105 mEq/l; CO₂ 25 mEq/l; BUN 15 mg/dl; and creatinine 1.0 mg/dl. Urinalysis revealed pH 5.0; SG 1.016; 4+ blood; 1+ protein; no glucose; many red blood cells; no casts; and multiple calcium oxalate crystals.

Which of the following studies is most likely to provide the correct diagnosis and should be done first in this situation?

- A. Non-contrast-enhanced helical CT scan

- B. Abdominal plain film
C. Intravenous pyelogram (IVP)
D. Ultrasonography

The correct answer is A. Non-contrast-enhanced helical CT scanning is the diagnostic method of choice for establishing the diagnosis of nephrolithiasis in most cases. The study can be combined with a flat plate to ensure that the stone is not radiolucent when there is a possibility of uric acid stones.

- Worster A, Preyra I, Weaver B, et al. The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. *Ann Emerg Med*. 2002;40(3): 280-6.

CASE 2: The helical CT scan demonstrates a 3 mm stone in the right ureter. A similar finding was seen on the abdominal flat plate.

Which of the following is the likely diagnosis?

- A. Calcium phosphate nephrolithiasis
B. Calcium oxalate nephrolithiasis
C. Uric acid nephrolithiasis
D. Cystine nephrolithiasis

The correct answer is B. The patient has hematuria, flank pain, a urine pH of 5, and calcium oxalate crystals on urinalysis. The helical CT scan demonstrates a 3 mm stone in the right ureter - all consistent with calcium oxalate urolithiasis.

A.

- Lemann J Jr. Composition of the diet and calcium kidney stones. *N Engl J Med.* 1993; 328(12):880-2.

CASE 3: What would be the best management approach at this time for this patient? (select all that apply)

- A. Urology consultation
- B. Hospitalization
- C. IV fluids
- D. IV antibiotics
- E. IV analgesics

The correct answers are B, C, and E. The patient needs hydration and ECF volume expansion to maintain urine flow. He cannot tolerate oral fluid, so IV therapy is indicated. The patient should also be treated with effective pain medications. IV NSAIDs are actually very effective in this situation.

- Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med.* 1992;327(16):1141-52.
- Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med.* 2002;346(2):77-84.

CASE 4: The patient experienced significant pain relief after IV analgesics and tolerated oral medications and fluids.

What orders would you write now? (select all that apply)

- A. Hospitalization
- B. Discharge to home
- C. Low calcium diet
- D. Maintain increased oral fluid intake
- E. Strain the urine
- F. Schedule a follow-up IVP for the following week
- G. Schedule a 24-hour urine collection for calcium and creatinine

The correct answers are B, D, and E. The patient tolerated medications and fluids orally and has pain relief. He can now be managed expectantly at home with increased fluid intake to await stone passages. Straining the urine with gauze increases the likelihood that a small stone

will be recovered for analysis.

- Levy FL, Adams-Huet B, Pak CV. Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. *Am J Med.* 1995;98(1):50-9.
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CASE 5: The patient was discharged and passed the stone 5 days later. No evidence of residual stone was seen on follow-up abdominal flat plate and CT scan. Analysis of the stone revealed it to be composed of 100% calcium oxalate. He now returns to the clinic to receive the results of the x-rays and stone analysis and to discuss prognosis and therapy.

What is your recommendation to patient at this time? (select all that apply)

- A. A complete metabolic work-up followed by appropriate treatment of any abnormalities and risk factors which are identified
- B. Measure the serum calcium and continue the high fluid intake but no other specific work-up or therapy as the likelihood of a second stone is less than 50% at 10 years
- C. Both of the above
- D. None of the above

The correct answers are A and B. A complete metabolic work-up followed by appropriate treatment of any abnormalities and risk factors which are identified

Also measure the serum calcium and the high fluid intake but no other specific workup or therapy as the likelihood of a second stone is less than 50% at 10 years. The relatively indolent course plus the availability of nonoperative therapy (such as lithotripsy) for most symptomatic stones has led some physicians to recommend a limited evaluation and therapy of the patient with a single calcium stone. However, the decision whether or not to undergo evaluation and therapy should be shared by the physician and patient.

- Levy FL, Adams-Huet B, Pak CV. Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. *Am J Med.* 1995;98(1):50-9.
- Segura JW, Preminger GM, Assimos DG, et al. Nephrolithiasis clinical Guidelines Panel

summary report with management of staghorn calculi. J Urol. 1994;151(6):1648-51.

CASE 6: The patient elected to take a conservative approach and not undergo extensive testing or specific therapy. He did increase his fluid intake to approximately 2.5 liters per day for several years and then paid less attention to his intake. He was clinically stone free for 5 years until 6 weeks ago when he again experienced right sided flank pain and hematuria and passed another small calcium oxalate. Follow-up IVP was normal and he was referred to the clinic for further evaluation. He is on no medications and his usual fluid intake is approximately 1.5 liters per day. He now agreed to undergo metabolic evaluation.

Which of the following studies should be included in this evaluation? (select all that apply)

- A. 24-hr urine for calcium
- B. 24-hr urine for uric acid
- C. 24-hr urine for oxalate
- D. 24-hr urine for citrate
- E. 24-hr urine for cystine
- F. 24-hr urine for creatinine
- G. 24-hr urine for phosphorus
- H. Serum calcium
- I. Serum uric acid
- J. Serum albumin
- K. Serum creatinine
- L. Serum electrolytes

The correct answers are A, B, C, D, F, H, J, K, and L. A metabolic workup for risk factors for calcium stone disease should include the following:

- Serum calcium concentration (risk factor = hypercalcemia)
- Serum albumin concentration (required to evaluate the serum calcium concentration)
- 24-hr urine calcium excretion (risk factor = hypercalciuria)
- 24-hr urine uric acid excretion (risk factor = hyperuricosuria)
- 24 hr urine oxalate excretion (risk factor = hyperoxaluria)
- 24-hr urine citrate excretion (risk factor = hypocitraturia)
- 24-hr creatinine excretion (required to evaluate completeness of the urine collections)

It is also useful to measure the serum electrolytes to rule out renal tubular acidosis as a cause of hypercalciuria and to measure the serum creatinine so that the creatinine clearance can be estimated.

- Levy FL, Adams-Huet B, Pak CV. Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. Am J Med. 1995;98(1):50-9.

CASE 7: In order to maximize the sensitivity of these measurements, the values for the metabolic work-up were obtained as the mean of three, 24-hr urine collection as follow:

Serum

Ca: 9.8 mg/dl
Na: 149 mEq/l
K 4.0 mEq/l
Cl 105 mEq/l
COH3- 25 mEq/l
BUN 12 mg/dl
Creatinine 1.0 mg/dl

Urine

Ca: 343 mg/day (normal <300 mg/day)
Na; 226 mEq/day
Oxalate 33 mg/day (normal <45 mg/day)
Citrate 256 mg/day (normal >320 mg/day)
Urate 678 mg/day (normal < 800 mg/day)
Creatinine 1500 mg/day (normal 20 mg/kg/day)

What is the most appropriate therapeutic regimen for this patient at this time? (select all that apply)

- A. Hydrochlorothiazide
- B. Potassium citrate
- C. Allopurinol
- D. Low calcium diet
- E. Moderate dietary sodium restriction
- F. High protein diet
- G. Water intake greater than 2 liters per day

The correct answers are A, B, E, and G. The patient has hypercalciuria and hypocitraturia. Appropriate treatment therefore should include hydrochlorothiazide and potassium citrate. Moderate sodium restriction is necessary to allow thiazides to produce sustained ECF volume contraction and maximal reduction in urinary calcium excretion. Increased fluid intake will lower urinary solute excretion.

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CASE 8: The patient was begun on hydrochlorothiazide, potassium citrate, increased fluid intake, and moderate sodium restriction. He returns two weeks later to review test results. Serum electrolytes are normal. The 24 hours urine values are: sodium 205 mEq; calcium 275 mg; citrate 544 mg; oxalate 30 mg; creatinine 1450 mg and uric acid 680 mg.

What do you recommend now?

- A. Re-emphasize the need for sodium restriction
- B. Add lasix
- C. Add amiloride

The correct answer is A. The patient has not complied with the recommendation to utilize moderate sodium restriction. For this reason, the hypocalciuric response to hydrochlorothiazide is blunted. Thus patient should be instructed to adhere to sodium restriction.

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CASE 9: The patient took his medication as instructed and maintained a high fluid intake and moderate sodium restriction. On this regimen he remained stone-free for the next 10 years. He indicates that his brother is concerned about the

possibility of an increased risk of calcium stone in the family.

Is there an increased risk for family members?

- A. Yes
- B. No

The correct answer is A. Yes, there is an increased likelihood of calcium stone disease in family members. The presence of a family history of nephrolithiasis, in about half of the individuals with hypercalciuria studied indicates that an inherited genetic defect is at least one likely cause of this condition.

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CASE 10: Which ONE of the following risk factors for calcium oxalate stone formation characterizes the urine of patients with medullary sponge kidney (MSK) and recurrent nephrolithiasis?

- A. Hypercalciuria
- B. Hyperuricosuria
- C. Hypocitraturia
- D. Reduced urine volume
- E. Increased magnesium excretion

The correct answer is C. Low urinary excretion of citrate and magnesium are the most typical metabolic disorders that distinguish MSK stone patients from idiopathic calcium-stone forming patients. In addition, anatomic abnormalities such as ectopic ducts, low levels of urinary inhibitors of stones seem to contribute to the pathogenesis of nephrolithiasis in patients with MSK.

- Yagisawa T, Kobayashi C, Hayashi T, et al. Contributory metabolic factors in the development of nephrolithiasis in patients with medullary sponge kidney. *Am J Kidney Dis* 2001;37 (6):1140-3.